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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/194,165	05/11/99	PERKES L	09143/005001

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	9

DATE MAILED: 10/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/194,165	Perkes, L.
Examiner	**Group Art Unit**
Patricia Patten	1651

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-37 is/are pending in the application.

Of the above, claim(s) 32-37 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

In consideration of the restriction requirement presented to Attorney Chad Hanson on 6/20/2000: The Examiner acknowledges Paper No. 6, which was a follow-up to the telephonic election. Nevertheless, a written restriction requirement was sent to the Attorney because the new Power of Attorney (Paper No. 6) was not matched up with the file at the time the written restriction requirement was sent (08/25/2000), and thus, the Examiner could not accept the election for the record at that time. Examiner regrets any confusion this may have caused.

Applicant's election without traverse of the restriction requirement in Paper No. 8 is acknowledged.

Claims 1-31 have been presented for examination on the merits.

Priority

In order to obtain priority benefits to an earlier PCT filing, the application must contain a specific reference to the prior PCT application(s) in the first sentence of the specification (37 CFR 1.78).

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant

application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The use of the trademark has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

Claims drawn to pharmaceutical compositions have further to be well defined and enabled in the specification as instantly filed. One of ordinary skill in the art, should, upon reading the specification, be able to make and use the invention as instantly claimed.

In the instant case, the specification as instantly filed does not support the breadth of Claims 1-14 and 22-31. Nowhere in the instant specification as filed, is there evidence displaying that any plant extract (or 'flavanoid source') admixed with a digestive enzyme would perform as effectively as PROVEXCV. Claims drawn to any combination of extracts with enzymes, besides the combination which is PROVEXCV, do not bear a reasonable correlation to the data provided by the Instant specification.

The state of the art regarding phytomedicine is highly unpredictable, and thus, lacking evidence regarding the effectiveness of **any one** of the plant extracts **alone** with a digestive enzyme is not enabled within the scope of the Instant disclosure. The instant specification has clearly shown that PROVEXCV has a positive effect on decreasing platelet aggregation.

However, there is not even one working example in the Instant specification that would indicate that admixtures of individual constituents of PROVEXCV, for example, grape skin extract admixed with a digestive enzyme would in fact display similar effects *in-vivo*. Lacking this guidance, one of ordinary skill in the art would have to rigorously test each constituent claimed individually in order to ascertain the effectiveness of each substance alone. This rigorous testing would necessarily require a substantial inventive contribution from the ordinary artesian, constituting an undue burden of trial and error experimentation.

The Instant specification is further lacking guidance which would necessarily allow the ordinary artisan to make the enabled composition of the present invention. The instant disclosure does not contain information regarding the plant extraction procedures. In leui of disclosure of extraction protocols , Applicant's have pointed out that the plant extracts can be obtained by several different companies which sell herbal extracts and/or supplements (Instant specification pp. 19). Indena Inc. (Please see copy of web page http://www.indena.it/pharmac.html) actually sells two types of ginkgo biloba extract; GINKGOSELECT and GINKGOSELECT PHYTOSOME. The ordinary artesian is left to his/her own judgement to chose which extract the Instant specification is referring to. In order to make such a judgement, unnecessary experimentation would have to be performed in order to assess the effectiveness of each respective extract. It is further not known how exactly to make the other constituents of PROVEXCV since the Instant specification lacks specific extraction protocols. It is unclear

whether the companies listed in the Instant specification all sell the same products with respect to the individual extracts (for example grape skin extract). Examiner attempted to search information regarding the grape skin extraction protocols from each company listed under 'Grape Skin Extract' on page 19 of the instant specification, was however unsuccessful. If in fact, the companies listed in the specification were to stop producing one of the extracts listed in the ingredients of PROVEXCV, how would one go about making it?

The art of phytomedicine is highly unpredictable as discussed *supra*. One of ordinary skill in the art could not be entirely sure that a grape skin extract from one company would be exactly the same grape extract from another company. If the grape skin extracts were extracted utilizing different extraction protocols such as an aqueous extraction and an alcoholic extraction, the phytomedicines would be expected to display different results in an individual due to the diversified phytochemical constituents in each respective extract. Taking the ginkgo extracts discussed earlier, it is known that ginkgo biloba plants produce effectively distinct products when subject to various extraction techniques. These different products may necessarily produce a myriad of different effects in an individual. For example, De Long et al. (US 6,030,621) taught that;

> "Great efforts have been made in the 1990's to enrich the active therapeutic components of Ginkgo biloba extract and to reduce its content of ginkgolic acids. At the same time, possibilities have been exploited to provide specific combinations of the effective components of Ginkgo biloba extract for different therapies. A combination of the ginkgolide components and the flavone glycosides will shift the active profile of the extract towards the anti-PAF-effects. By contrast, a combination of the

bilobalide and the flavone glycosides will apply the active profile more effectively against encephalopathies, cerebral edemas, demyelinating neuropathies and myelopathies....." (Col.2, lines 10-21)

Since any given biological source contains thousands of extractable compounds, each with it's own particular extraction properties, the nature of the resulting "extract" will depend on the conditions of the extraction and the solvent used. For example, is the extract obtained via extraction with water, a polar solvent, a non-polar solvent, or an acid or base, at what temperature, or is it a squeezed extract? It is well accepted in the natural products and herbal art, that extraction of a biological source with one of various distinct solvents has a profound impact on the final product with respect to the presence, amounts, and/or ratios of active ingredients obtained, and, thus, on the ability of the "extract" to provide the desired functional effect(s) claimed and/or disclosed.

Clearly, plants such as gingko biloba contain a myriad of phytochemicals which have distinct pharmacological capabilities. Thus, since the Instant specification as filed is not entirely clear as to exactly what ginkgo biloba, grape seed, grape skin, bilberry or citrus extracts are used in the combination to make PROVEXCV, it would require undue experimentation in order to create a composition which would display parallel results which Applicant's have provided in the disclosure regarding PROVEXCV.

Since each individual extraction procedure would necessarily bring about a different product, it is unpredictable how the difference would effect an individual *in-vivo*. There is no guidance or direction presented to direct one to determine which isoflavones would work in the broadly claimed invention which is a complex and unpredictable art.

Therefore because of the large number of inoperable embodiments claimed, it would require a substantial inventive contribution of the ordinary artisan to practice the claimed invention. It may be true the Applicant is able to make the invention, however the application is directed toward one of ordinary skill in the art. It is not seen the claims are set forth in clear, concise and exact terms to enable someone other than the Applicant to make the invention **which is a requirement of the statute**. It has been well established that disclosure in an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves." In re Gardner et al., 166 USPQ 138 (CCPA 1970).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 and 22-31 are rejected for the recitation of 'a flavanoid source.' It is unclear what a 'flavanoid source' is. The meets and bounds of the claim language are not clearly delineated upon recitation of 'flavanoid source.' Consequently, a 'flavanoid source' may be interpreted to mean any naturally occurring plant or vegetable substance. Furthermore, a 'flavanoid source' could be an orange tree for example, or a place of manufacture. Correction is necessary.

Claim 19 recites 'phytosome.' It is unclear what a form of a phytosome would be.

Claims 23 and 24 lack antecedent basis in Claim 22. Claims 23 and 24 both recite where the supplement comprises a 'plurality of flavanoid sources' or PROVEXCV2. Since Claim 22 recites '**an** unfermented flavanoid source' and **an** enzyme, Claims 23 and 24 broaden rather than limit Claim 22.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-11 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Balch et al. (1997). Claims 1-5, 9-11 and 22 are drawn to a composition comprising a

flavanoid and an enzyme, wherein said flavanoid are specific plant extracts such as quercetin, and where the enzyme is a digestive enzyme such as bromelain or a fungal protease.

Compositions comprising flavanoids and digestive enzymes were known at the time of the Instant application. For example, Balch et al. (1997) explained that quercetin, a bioflavanoid and bromelain, a naturally occurring digestive enzyme, "should be taken in conjunction to enhance absorption" and added that quercetin and bromelain are synergists.

The composition claims recite "said supplement is effective for inhibiting platelet activity...". This is merely considered functional intended use language, and holds no patentable weight. "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 195 USPQ 430, 433 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 21-22 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaynor et al. (US 5,904,924) in view of Balch et al. (1997) and further in view of Handel et al. (US 5, 387,422). Claims 6-8, 21 and 23-24 are drawn to where the flavanoid source is a specific extract such as grape, bilberry or ginkgo biloba, or where the composition comprises PROVEXCV or PROVEXCV2, or where the supplement contains grape seed extract, grape skin extract, ginkgobiloba extract, bilberry extract, quercetin, fungal protease, acid stable protease and bromelain. Claims are further drawn to specific forms of the composition, such as a powder, a liquid or a pill.

Gaynor et al. (US 5,904,924) created a composition comprising grape seed extract, grape skin extract, bilberry, and ginkgo biloba extract (Please see Table in Col.4). Gaynor et al. taught that quercetin was a naturally occurring, intrinsic element to the composition (Col.3, ins 52-58). Although Gaynor et al. did not specifically teach 'bilberry extract' the extract would have been intrinsic to the bilberry composition disclosed by Gaynor et al.

The teachings of Balch et al. (1997) were discussed *supra*. Balch et al. further taught that digestive enzymes, such as bromelain (Balch et al. do not specifically mention bromelain on the pages Examiner refers to, but mentions fruit enzymes such as pineapple, which are known to contain bromelain (pp.21, Col.1)), pepsin, pancreatin and fungal proteases, such as proteases obtained for Aspergillus were advantageously combined with supplements in order to aid digestion (pp. 48-49). It was known that fungal proteases obtained by Aspergillus were also acid stable as taught by Handel et al. (US 5,387,422). "...An **acid protease fungal enzyme** obtained from *Rhizopus niveus* or *Aspergillus niger var. macropourus*...." (Col.1, lines 12-15).

One of ordinary skill in the art would have been motivated to combine the composition disclosed by Gaynor et al. with a protease composition comprising a fungal protease, an acid stable protease and bromelain in order to effectively aid digestion of the composition. Balch et al. had already disclosed that digestive enzymes such as bromelain and fungal proteases were advantageously combined with supplements in order to "aid digestion of foods and absorption of nutrients, especially protein" (pp.48, Col.1). Thus, one would have had a reasonable expectation that combining the proteases taught by Balch et al. with the composition disclosed by Gaynor et al. would have increased the effectiveness of the herbal composition due to the proteolytic activity of the enzymes, consequently creating a product which had better digestibility and bioavailability.

One of ordinary skill in the art would have been motivated to have modified the proportions of active ingredients in the composition in order to enable the content of the preparation to be matched with the demands and needs of individuals which needed treatment.

Varying individual levels of constituents in a pharmaceutical preparation was considered routine experimental procedure at the time of the instant invention. It would have been well within the purview of the ordinary artisan to have created different forms of the composition, such as pills or powders. Creating different forms of a composition was simply a matter of design choice, allowing for ease of administration of the herbal composition as well as offering a choice of supplement form to the consumer.

Claims 25-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pace-Asciak et al. (1995) in view of Balch et al. (1997). Claims 25-31 are drawn to a method of inhibiting platelet activity or LDL cholesterol oxidation in a mammal comprising a flavanoid source and an enzyme in varying dosage levels.

It was known at the time of the instant application that grapes (grape seed and grape skin) contained phytochemicals such as quercetin and resveratrol which were shown to decrease platelet aggregation as evidenced by the entirety of the reference disclosed by Pace-Asciak et al. (1995).

The teachings of Balch et al. were discussed *supra.*

One of ordinary skill in the art would have had a reasonable expectation that a composition containing extracts from grapes, such as grape seed or grape skin would intrinsically

contain phytochemicals such as resveratrol and quercetin which were known to decrease platelet activity *in vivo*. Thus, it would not have required a substantial inventive contribution to have added other ingredients to an already pharmaceutically effective phytochemicals in order to achieve similar effects. One would have been motivated to have added a digestive enzyme such as bromelain, since, as Balch et al. discussed supra, bromelain and quercetin acted synergistically in providing a more bioavailable quercetin *in vivo*.

Varying individual levels of constituents in a pharmaceutical preparation as well as varying physical forms of pharmaceuticals were considered routine experimental procedures at the time of the instant invention. It would have been well within the purview of the ordinary artisan to have created different forms of the composition, such as pills or powders. Creating different forms of a composition was simply a matter of design choice, allowing for ease of administration of the herbal composition as well as offering a choice of supplement form to the consumer.

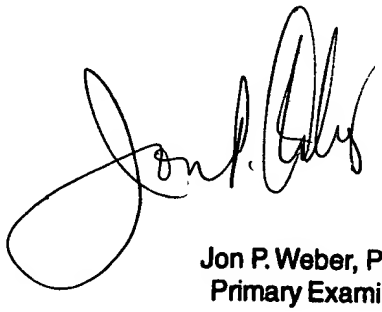
From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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